PATENT SPECIFICATION

NO DRAWINGS

935,381

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International Classification:—**C07c, d.** (A61k).

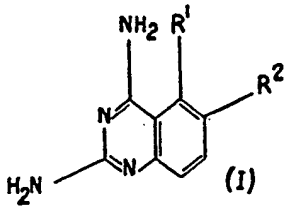
COMPLETE SPECIFICATION

2,4-Diaminoquinazolines and their preparation

We, THE WELLCOME FOUNDATION LIMITED, a British Company of 183—193 Euston Road, London, N.W.1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is an improvement in or modification of the invention claimed in patent No. 806,772.

This invention provides in one aspect a new method for making 2,4-diaminoquinazolines of formula (I) which have antibacterial activity.

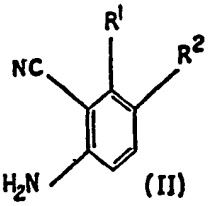


(I)

In this formula, R^1 is a lower alkyl group and R^2 is a hydrogen atom or a lower alkyl group and R^1 may be a hydrogen atom when R^2 is a lower alkyl group, R^1 and R^2 together having not more than 10 carbon atoms, or R^1 and R^2 together form an alkylene chain having 3 or 4 carbon atoms.

2,4 - Diamino - 6 - methylquinazoline and 2,4 - diamino - 6 - ethylquinazoline are known and were made by the successive chlorination and amination of the corresponding 2,4-dihydroxyquinazolines. Whether or not 2,4-diaminoquinazolines can be made by this old method depends on the reactivities of the individual compounds concerned, but the new method provided by this invention is a general method which can be used for making all compounds of formula (I).

According to the method of the invention, an anthranilonitrile of formula (II), wherein R^1 and R^2 are as defined above, is reacted with dicyandiamide and the 2,4-diaminoquinazoline of formula (I) is recovered from the reaction mixture.



(II)

This invention provides in another aspect certain new 2,4-diaminoquinazolines of formula (I), which have superior antibacterial activity and are described in Examples 2 to 7 below.

The novel compounds may be presented in antibacterial preparations prepared by any well known pharmaceutical method.

For oral administration, fine powders or granules of the compounds may contain diluents and dispersing and surface active agents, and may be presented in capsules or cachets in the dry state or in a non-aqueous suspension, when a suspending agent may be included; in tablets when binders and lubricants may be included; or in a syrup or an oil or in a water/oil emulsion, when flavouring, preserving, suspending, thickening and emulsifying agents may be included. The granules or the tablets may be coated.

For parenteral administration, the compounds may be presented in aqueous injection solutions which may contain antioxidants, buffers, agents which solubilise a relatively insoluble compound, and solutes which render the solution isotonic with the blood. Extemporaneous injection solutions may be prepared from sterile pills, granules or tablets which may contain diluents, dispersing and surface active agents, binders and lubricants.

The compounds may be presented in suppositories or pessaries by incorporation in a suppository base; for external use, in oint-

[*Price 4s. 6d.*]

ments by incorporation in fatty or water-miscible substances or in creams by incorporation in water or an oil, when an emulsifying agent may be included.

Solutions of the novel compounds are potent antibacterials for topical use—the compounds being used as their soluble salts in concentrations in the order of 0.01 to 1%.

The compounds may be presented as the sole active ingredient in a preparation, or may be presented in combination with antibiotics or other antibacterial agents.

The following examples illustrate the invention. Temperatures are given in degrees Celsius.

EXAMPLE 1

2,4-Diamino-6-ethylquinazoline

5 g. 5-Ethylisatin β-oxime was heated in an oil bath to 210°. At this temperature, decomposition took place and the 2-amino-5-ethylbenzonitrile distilled over. The distillate was dissolved in absolute ether and precipitated as the hydrochloride.

1.1 g. 2 - Amino - 5 - ethylbenzonitrile hydrochloride was thoroughly mixed with 0.6 g. dicyandiamide and heated to 150° and the temperature kept at 150—160° for 5 minutes. The addition of 15 ml. concentrated hydrochloric acid dissolved the reaction mixture which after boiling for 5 minutes was poured over ice and made alkaline with sodium hydroxide. The precipitate was filtered, washed and recrystallised from water. The melting point of 2,4 - diamino - 6 - ethylquinazoline was 223—224°.

EXAMPLE 2

2,4-Diamino-5,6-trimethylenequinazoline

12 g. 5 - Acetylamino - 4 - bromoindane and 5 g. cuprous cyanide were refluxed in 13 ml. pyridine for 5 hours. The reaction mixture was poured into 50 ml. 7 *N* ammonium hydroxide and extracted with a mixture of 100 ml. ether and 100 ml. benzene. The organic layer was washed with 3×35 ml. diluted ammonium hydroxide followed by 2×35 ml. 2 *N* hydrochloric acid and finally with water. After drying over calcium sulphate, the ether-benzene mixture was filtered and evaporated to 75 ml. The product, 5-acetylamino - 4 - cyanoindane, crystallised out and was collected. It melted at 137—138°.

4.5 g. Acetylamino - 4 - cyanoindane was dissolved in 100 ml. absolute alcohol containing 2 g. sodium methoxide and refluxed overnight. The reaction mixture was poured over ice in the presence of sufficient acetic acid to neutralise the sodium hydroxide. The 5-amino - 4 - cyanoindane was extracted with ether and precipitated as the hydrochloride from this solution.

3.4 g. 5 - Amino - 4 - cyanoindane hydrochloride was thoroughly mixed with 2 g. dicyandiamide and fused at 160—165° for 15 minutes. The reaction mixture was then dissolved in 50 ml. concentrated hydrochloric acid, poured over ice and made alkaline with sodium hydroxide. The precipitate was washed and recrystallised from alcohol. This product then was dissolved in very dilute formic acid and put through a Dowex-1 (formate) column. The effluent was neutralised and the crystalline 2,4-diamino-5,6-trimethylenequinazoline collected. The melting point was 288°.

EXAMPLE 3

2,4-Diamino-5-methylquinazoline

2 - Amino - 6 - methylbenzonitrile was prepared as described in Example 1 using 4-methylisatin.

6 g. 2 - Amino - 6 - methylbenzonitrile was thoroughly mixed with 6 g. dicyandiamide and fused at 150—160° for 15 minutes in an oil bath. The reaction mixture was dissolved in 150 ml. water, cooled and made alkaline with sodium hydroxide. The resulting 2,4 - diamino - 5 - methylquinazoline, after recrystallisation from water, melted at 212—213°.

EXAMPLE 4

2,4-Diamino-6-n-propylquinazoline

8 g. 2 - Amino - 5 - n - propylbenzonitrile was prepared through decomposition of the corresponding isatin β-oxime.

8 g. 2 - Amino - 5 - n - propylbenzonitrile hydrochloride was thoroughly mixed with 3.3 g. dicyandiamide and worked up as in Example 1. The crude 2,4-diamino-6-n-propylquinazoline was recrystallised from water. It melted at 194—195°.

EXAMPLE 5

2,4-Diamino-6-n-butylquinazoline

4 g. 5 - n - Butylisatin β - oxime was decomposed at 235°. The resultant 2-amino-5-n-butylbenzonitrile was dissolved in ether and the hydrochloride precipitated.

1.6 g. 2 - Amino - 5 - n - butylbenzonitrile hydrochloride was fused with 650 mg. dicyandiamide at 155° for 10 minutes. The reaction mixture was dissolved by the addition of 30 ml. concentrated hydrochloric acid and 20 ml. alcohol. After being poured over ice, it was made alkaline with sodium hydroxide. The precipitate was recrystallised from water. 2,4 - Diamino - 6 - n - butylquinazoline melted at 191—192°.

EXAMPLE 6

2,4-Diamino-5,6-tetramethylenequinazoline

12 g. 4,5 - Tetramethyleneisatin β - oxime was decomposed as in Example 1. The hydrochloride of the 2 - amino - 5,6,7,8 - tetrahydro - 1 - naphthonitrile was precipitated and collected. 3.5 g. 2 - Amino - 5,6,7,8-tetrahydro - 1 - naphthonitrile was thoroughly mixed with 1.5 g. dicyandiamide and fused at 165° for 10 minutes. The reaction mixture was treated as in Example 1 and the crude 2,4 - diamino - 5,6 - tetramethylenequinazoline recrystallised from formamide with the addition of water. The compound melted at 240°.

EXAMPLE 7

2,4-Diamino-5-ethylquinazoline

4.8 g. 4-Ethylisatin β-oxime was decomposed and the distillate after being dissolved in ether was precipitated as the hydrochloride.

1.8 g. 2 - Amino - 6 - ethylbenzonitrile was thoroughly mixed with 850 mg. dicyandiamide and heated at 155° for 5 minutes. The reaction mixture was dissolved in concentrated hydrochloric acid and the compound precipitated with sodium hydroxide. After repeated recrystallisation from water the 2,4-diamino-5-ethylquinazoline was obtained as a white crystalline material.

WHAT WE CLAIM IS:—

1. A method for making a 2,4-diaminoquinazoline of formula (I) characterised in that an anthranilonitrile of formula (II) is reacted with dicyandiamide and the 2,4-diaminoquinazoline of formula (I) is recovered from the reaction mixture.

2. A method for making a 2,4-diaminoquinazoline of formula (I) substantially as described in any of the examples.

3. A 2,4 - diaminoquinazoline of formula (I) when made by the method claimed in either of claims 1 and 2.

4. 2,4 - Diamino - 5,6 - trimethylenequinazoline.

5. 2,4 - Diamino - 5 - methylquinazoline.

6. 2,4 - Diamino - 6 - n - propylquinazoline.

7. 2,4 - Diamino - 6 - n - butylquinazoline.

8. 2,4 - Diamino - 5,6 - tetramethylenequinazoline.

9. 2,4 - Diamino - 5 - ethylquinazoline.

10. An antibacterial preparation containing a 2,4-diaminoquinazoline as claimed in any of claims 4 to 9, in association with a pharmaceutically acceptable carrier.

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